Amendments to the Specification:

Please amend the specification as follows:

Please amend the text, including the title, at the top of page 1 as follows:

Method of Measuring Activation of Effector Cells ~~Cytokine production-inducing antibody~~

Background of the Invention

Field of the Invention

Please replace the paragraph at page 1, lines 3-15, with the following amended paragraph:

The present invention relates to a method for measuring the activation of an effector cell belonging to the immune system, or modified in vitro, by means of a monoclonal (MoAb) or polyclonal antibody, characterized in that it comprises bringing CD16 receptor-expressing cells into contact in a reaction medium in the presence of the antibody and of the antigen for said antibody, and measuring the amount of at least one cytokine produced by the CD16 receptor-expressing cell. The invention also relates to the selection of antibodies having the characteristic of inducing the expression of cytokines and of interleukins, in particular IFNγ or [[IL-2]] IL-2.

Please insert after the paragraph at page 2, lines 29-36, the following caption:

Description of Related Art

Please insert before the paragraph at page 3, lines 23-33, the following caption:

Summary of the Invention

Please replace the paragraph at page 3, lines 23-33, with the following amended paragraph:

In the context of the invention, it has been found that the binding of an antibody to its ligand can induce activation of CD16-transfected Jurkat cells, inducing [[IL2]] IL-2 secretion. A strong correlation is observed between the secretion of [[IL2]] IL-2 by Jurkat CD16 and the CD16-mediated ADCC activity of the effector cells. In addition, we have observed that the same antibody directed against a given antigen is completely ineffective when it is produced

in mouse myeloma lines, whereas it is found to be very effective when it is produced in other cell lines.

Please replace the paragraph at page 4, lines 1-5, with the following amended paragraph:

The invention therefore proposes the use of antibodies selected using a Jurkat CD16 test, by measuring secreted [[IL2]] IL-2 or other cytokines, which makes it possible to guarantee the biological activity of said antibodies for therapeutic use.

Please insert after the paragraph at page 4, lines 1-5, the following text:

FIG. 1 is a description of the MNC ADCC assay.
FIG. 2 is a description of the NK ADCC assay.
FIG. 3 is a description of the NK ADCC and resulting inhibition of the anti-CD16 "3G8".
FIG. 4 is a description of the Jurkat CD16 assay.
FIG. 5 shows results of the Jurkat CD16 assay.
FIG. 6 shows release of cytokine (IL-2, IFN and TNF) by leukocytes that are antibody-activated in the presence of their target.
FIG. 7 shows release of cytokine (IFN, TNF) by NK cells that are antibody-activated in the presence of their target (LFB-R297-RBC).
FIG. 8 shows release of IL2 by Jurkat CD16 activated by an anti-CD20.
FIG. 9 shows release of IL2 by Jurkat CD16 activated by an anti-D.
FIG. 10 shows a line of correlation between the ADCC (Tegelin 500 µg/well and anti-D at 7.5 ng/well) and the Jurkat IL2 assay.
FIG. 11 show secretion of IL-8 by mononuclear cells.
FIG. 12 shows induction of TNF alpha, IL-6 and TGF beta secretion by mononuclear cells.
FIG. 13 shows induction of cytokine secretion by polymorphonuclear cells.
FIG. 14 shows induction of IFN gamma, TNF alpha and IP10 secretion by NK cells.

Please replace the paragraph at page 5, lines 4-9, with the following amended paragraph:

Preferably, the amount of interleukin [[IL2]] IL-2 secreted reflects the quality of the antibody bound by the CD16 receptor as regards its antigen-binding integrity (Fc function) and

effectiveness (antigenic site). The measurement of the amount of [[IL2]] IL-2 is correlated with an ADCC-type activity.

Please replace the paragraph at page 7, lines 11-27, with the following amended paragraph:

In a particular embodiment, the antibody of the invention is capable of inducing the secretion of at least one cytokine by a leukocytic cell, in particular of the NK (natural killer) family, or by cells of the monocyte-macrophage group. In general, for selecting the antibodies, use is made of a Jurkat-type line or another line transfected with an expression vector encoding the Fc receptor, including CD16, CD32 and CD64, as effector cell. Preferably, for selecting the antibodies, a Jurkat line transfected with an expression vector encoding the CD16 receptor is used as effector cell. This line is particularly advantageous since it is immortalized and develops indefinitely in culture media. The amount of interleukin [[IL2]] IL-2 secreted reflects the quality of the antibody bound by the CD16 receptor as regards its antigen-binding integrity (Fc function) and effectiveness (antigenic site).

Please replace the paragraph at page 9, lines 10-17, with the following amended paragraph:

Preferably, the antibody selected has the ability to induce the secretion of IL-2 by the CD16 receptor-expressing effector cells of the immune system. The amount of interleukin [[IL2]] IL-2 secreted reflects the quality of the antibody bound by the CD16 receptor as regards its antigen-binding integrity (Fc function) and effectiveness (antigenic site). The measurement of the amount of [[IL2]] IL-2 is correlated with an ADCC-type activity.

Please replace the paragraph at page 12, lines 9-11, with the following amended paragraph:

Comments: the antibodies that are positive in ADCC-NK induce secretion of [[IL2]] IL-2 in the presence of Jurkat CD16 and of their target.

Please replace the paragraph at page 12, lines 34-35, with the following amended paragraph:

FIG. 8: Release of [[IL2]] IL-2 by Jurkat CD16 activated by an anti-CD20

Please replace the paragraph at page 13, lines 5-6, with the following amended paragraph:

FIG. 9: Release of [[IL2]] IL-2 by Jurkat CD16 activated by an anti-D

Please replace the paragraph at page 13, lines 9-14, with the following amended paragraph:

B--Jurkat CD16 cells were mixed with various anti-D antibodies in the presence of Rhesus+red blood cells and of PMA. After an overnight incubation period, the release of IL-2 into the supernatant was quantified by ELISA. DF5 expressed in YB2/0 and T125 expressed in CHO Lec13 induce strong secretion of [[IL2]] IL-2.

Please replace the paragraph at page 13, lines 16-18, with the following amended paragraph:

FIG. 10: Line of correlation between the ADCC (Tegeline 500 µg/well and anti-D at 7.5 ng/well) and the Jurkat [[IL2]] IL-2 assay.

Please replace the paragraph between pages 13-14 with the following amended paragraph:

This assay evaluates the ability of the anti-D antibodies to bind to the CD16 receptor (Fc gamma RIII) expressed on Jurkat CD16 cells, and to induce [[IL2]] IL-2 secretion.

Please replace the paragraph at page 14, line 14, with the following amended paragraph:

[[IL2]] IL-2 assay kit: Quantikine from R/D.

Please replace the paragraph at page 14, lines 29-31, with the following amended paragraph:

Then, centrifugation of the plates, removal of 100 µl of supernatants and assaying of [[IL2]] IL-2 with the commercial kit. Reading at 450 nm.

Please replace the paragraph at page 16, lines 18-22, with the following amended paragraph:

The same samples are evaluated by ADCC and in the Jurkat [[IL2]] IL-2 assay. The results are expressed as percentage of the reference antibody "LFB-R297". The curve for correlation between the two techniques has a coefficient of r2=0.9658 (FIG. 10).

Please replace the paragraph at page 16, lines 24-28, with the following amended paragraph:

In conclusion, these data show the importance of post-translational modifications of the structure of the antibodies in terms of their FcgammaRIII-specific ADCC activity. The release of cytokines such as IL-2 reflects this activity.

Please replace the caption at page 16, lines 30-31, with the following amended caption:

EXAMPLE 3 : Activation of NK cells and Production of [[IL2]] IL-2 and of IFNγ

Please replace the paragraph at page 16, lines 35-38, with the following amended paragraph:

[[IL2]] IL-2 induces activation of T lymphocytes and of the NK cells themselves, which can go as far as stimulation of cell proliferation. IFNγ stimulates the activity of CTLs and can enhance the activity of macrophages.

Please replace the paragraph at page 18, lines 10-14, with the following amended paragraph:

6.2 The monoclonal antibody R297 and the polyclonal antibody WinRho induce a very weak, but greater than AD1, secretion of [[IL2]] IL-2, of IFN gamma, of IP10 and of TNF by polymorphonuclear cells. This secretion is antibody-concentration dependent (FIG. 13).